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Even still a further aspect of the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein
 5 comprises a SOCS box in its C-terminal region wherein the SOCS box comprises the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO:51)

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wherein: X_1 is L, I, V, M, A or P;
 X_2 is any amino acid residue;
 X_3 is P, T or S;
 X_4 is L, I, V, M, A or P;
 X_5 is any amino acid;
 X_6 is any amino acid;
 X_7 is L, I, V, M, A, F, Y or W;
 X_8 is C, T or S;
 X_9 is R, K or H;

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X_{10} is any amino acid;
 X_{11} is any amino acid;
 X_{12} is L, I, V, M, A or P;
 X_{13} is any amino acid;
 X_{14} is any amino acid;
 X_{15} is any amino acid;
 X_{16} is L, I, V, M, A, P, G, C, T or S;
 $[X]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids
 and wherein the sequence X_i may comprise the same or different amino
 acids selected from any amino acid residue;
 X_{17} is L, I, V, M, A or P;
 X_{18} is any amino acid;

X_{19} is any amino acid;

X_{20} L, I, V, M, A or P;

X_{21} is P;

X_{22} is L, I, V, M, A, P or G;

X_{23} is P or N;

$[X_j]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_j may comprise the same or different amino acids selected from any amino acid residue;

X_{24} is L, I, V, M, A or P;

X_{25} is any amino acid;

X_{26} is any amino acid;

X_{27} is Y or F;

X_{28} is L, I, V, M, A or P;

15 and a protein:molecule interacting region such as but not limited to one or more of an SH2 domain, WD-40 repeats and/or ankyrin repeats N-terminal of the SOCS box.

Another aspect of the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a
20 derivative, homologue, analogue or mimetic thereof or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein exhibits the following characteristics:

(i) comprises a SOCS box in its C-terminal region having the amino acid sequence:

25 $X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_i]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO: 51)

wherein: X_1 is L, I, V, M, A or P;

X_2 is any amino acid residue;

30 X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

protein:molecule interacting domain in a region N-terminal of the SOCS box.

Preferably, the SOCS molecules modulate signal transduction such as from a cytokine or hormone or other endogenous or exogenous molecule, a microbe or microbial product, an antigen or a parasite.

More preferably, the SOCS molecule modulate cytokine mediated signal transduction.

Still another aspect of the present invention comprises a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or comprises a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein exhibits the following characteristics;

- (i) is capable of modulating signal transduction;
- (ii) comprises a SOCS box in its C-terminal region having the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_i]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO:51)

- wherein:
- X_1 is L, I, V, M, A or P;
 - X_2 is any amino acid residue;
 - X_3 is P, T or S;
 - X_4 is L, I, V, M, A or P;
 - X_5 is any amino acid;
 - X_6 is any amino acid;
 - X_7 is L, I, V, M, A, F, Y or W;
 - X_8 is C, T or S;
 - X_9 is R, K or H;
 - X_{10} is any amino acid;
 - X_{11} is any amino acid;
 - X_{12} is L, I, V, M, A or P;

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Another aspect of the present invention contemplates a protein or a derivative, homologue, analogue or mimetic thereof comprising a SOCS box in its C-terminal region and a SH2 domain, WD-40 repeats or ankyrin repeats N-terminal of the SOCS box.

5 Still yet another aspect of the present invention provides a protein or a derivative, homologue, analogue or mimetic thereof exhibiting the following characteristics:

(i) comprises a SOCS box in its C-terminal region having the amino acid sequence:

10 $X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO: 51)

wherein: X_1 is L, I, V, M, A or P;

X_2 is any amino acid residue;

15 X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is L, I, V, M, A, F, Y or W;

20 X_8 is C, T or S;

X_9 is R, K or H;

X_{10} is any amino acid;

X_{11} is any amino acid;

X_{12} is L, I, V, M, A or P;

25 X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is any amino acid;

X_{16} is L, I, V, M, A, P, G, C, T or S;

$[X]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids

30 and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

(ii) comprises a SOCS box in its C-terminal region having the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_i]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO: 51)

5

wherein: X_1 is L, I, V, M, A or P;

X_2 is any amino acid residue;

X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

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X_5 is any amino acid;

X_6 is any amino acid;

X_7 is L, I, V, M, A, F, Y or W;

X_8 is C, T or S;

X_9 is R, K or H;

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X_{10} is any amino acid;

X_{11} is any amino acid;

X_{12} is L, I, V, M, A or P;

X_{13} is any amino acid;

X_{14} is any amino acid;

20

X_{15} is any amino acid;

X_{16} is L, I, V, M, A, P, G, C, T or S;

$[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

25

X_{17} is L, I, V, M, A or P;

X_{18} is any amino acid;

X_{19} is any amino acid;

X_{20} L, I, V, M, A or P;

X_{21} is P;

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X_{22} is L, I, V, M, A, P or G;

X_{23} is P or N;

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides a new family of modulators of signal transduction. As the initial members of this family suppressed cytokine signalling, the family is referred to as the "suppressors of cytokine signalling" family of "SOCS". The SOCS family is defined by the presence of a C-terminal domain referred to as a "SOCS box". Different classes of SOCS molecules are defined by a motif generally but not exclusively located N-terminal to the SOCS box and which is involved by protein:molecule interaction such as protein:DNA or protein:protein interaction. Particularly preferred motifs are selected from an SH2 domain, WD-40 repeats and ankyrin repeats.

WD-40 repeats were originally recognised in the β -subunit of G-proteins. WD-40 repeats appear to form a β -propeller-like structure and may be involved in protein-protein interactions. Ankyrin repeats were originally recognised in the cytoskeletal protein ankyrin.

Members of the SOCS family may be identified by any number of means. For example, SOCS1 to SOCS3 were identified by their ability to suppress cytokine-mediated signal transduction and, hence, were identified based on activity. SOCS4 to SOCS15 were identified as nucleotide sequences exhibiting similarity at the level of the SOCS box.

The SOCS box is a conserved motif located in the C-terminal region of the SOCS molecule. In accordance with the present invention, the amino acid sequence of the SOCS box is:

$$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_i]_n X_{17} X_{18} X_{19} X_{20} \\ X_{21} X_{22} X_{23} [X_j]_m X_{24} X_{25} X_{26} X_{27} X_{28} \text{ (SEQ ID NO: 51)}$$

wherein: X_1 is L, I, V, M, A or P;
 X_2 is any amino acid residue;
 X_3 is P, T or S;
 X_4 is L, I, V, M, A or P;
 X_5 is any amino acid;

mouse SOCS-10 characterised by mb14d12, mb40f06, mg89b11, mq89e12, mp03g12 and vh53c11;

human SOCS-11 characterised by zt24h06 and zr43b02;

human SOCS-13 characterised by EST59161;

mouse SOCS-13 characterised by ma39a09, me60c05, mi78g05, mk10c11, mo48g12, mp94a01, vb57c07 and vh07c11; and

human SOCS-14 characterised by mi75e03, vd29h11 and vd53g07;

or a derivative or homologue of the above ESTs characterised by a nucleic acid molecule being capable of hybridizing to any of the listed ESTs under low stringency conditions at 42°C.

In another embodiment, the nucleotide sequence encodes the following amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_1]_n X_{17} X_{18} X_{19} X_{20}$

$X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO:51)

wherein: X_1 is L, I, V, M, A or P;

X_2 is any amino acid residue;

X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is L, I, V, M, A, F, Y or W;

X_8 is C, T or S;

X_9 is R, K or H;

X_{10} is any amino acid;

X_{11} is any amino acid;

Still another embodiment of the present invention contemplates an isolated polypeptide or a derivative, homologue, analogue or mimetic thereof comprising a SOCS box in its C-terminal region.

5 Preferably the polypeptide further comprises a protein:molecule interacting domain such as a protein:DNA or protein:protein interacting domain. Preferably, this domain is located N-terminal of the SOCS box. It is particularly preferred for the protein:molecule interacting domain to be at least one of an SH2 domain, WD-40 repeats and/or ankyrin repeats.

10 Preferably, the signal transduction is mediated by a cytokine selected from EPO, TPO, G-CSF, GM-CSF, IL-3, IL-2, IL-4, IL-7, IL-13, IL-6, LIF, IL-12, IFN γ , TNF α , IL-1 and/or M-CSF. Preferred cytokines are IL-6, LIF, OSM, IFN- γ or thrombopoietin.

More preferably, the protein comprises a SOCS box having the amino acid sequence:

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$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X]_m X_{24} X_{25} X_{26} X_{27} X_{28}$ (SEQ ID NO: 51)

wherein: X_1 is L, I, V, M, A or P;

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X_2 is any amino acid residue;

X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

X_5 is any amino acid;

X_6 is any amino acid;

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X_7 is L, I, V, M, A, F, Y or W;

X_8 is C, T or S;

X_9 is R, K or H;

X_{10} is any amino acid;

X_{11} is any amino acid;

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X_{12} is L, I, V, M, A or P;

X_{13} is any amino acid;